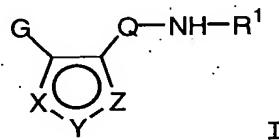


CLAIMS

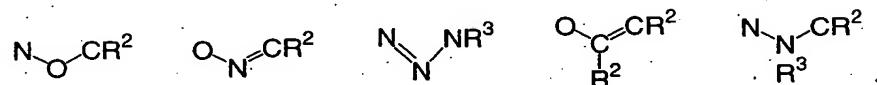
We claim:

1. A compound having the formula



wherein:

X-Y-Z is selected from one of the following:



$R^1$  is H,  $CONH_2$ ,  $T_{(n)}-R$ , or  $T_{(n)}-Ar^2$ ;

$R$  is an aliphatic or substituted aliphatic group;

$n$  is zero or one;

$T$  is  $C(=O)$ ,  $CO_2$ ,  $CONH$ ,  $S(O)_2$ ,  $S(O)_2NH$ ,  $COCH_2$  or  $CH_2$ ;

each  $R^2$  is independently selected from hydrogen, -R,

- $CH_2OR$ , - $CH_2OH$ , - $CH=O$ , - $CH_2SR$ , - $CH_2S(O)_2R$ ,

- $CH_2(C=O)R$ , - $CH_2CO_2R$ , - $CH_2CO_2H$ , - $CH_2CN$ , - $CH_2NHR$ ,

- $CH_2N(R)_2$ , - $CH=N-OR$ , - $CH=NNHR$ , - $CH=NN(R)_2$ ,

- $CH=NNHCOR$ , - $CH=NNHCO_2R$ , - $CH=NNHSO_2R$ , -aryl,

-substituted aryl, - $CH_2(aryl)$ , - $CH_2$ (substituted

aryl), - $CH_2NH_2$ , - $CH_2NHCOR$ , - $CH_2NHCONHR$ ,

- $CH_2NHCON(R)_2$ , - $CH_2NRCOR$ , - $CH_2NHCO_2R$ , - $CH_2CONHR$ ,

- $CH_2CON(R)_2$ , - $CH_2SO_2NH_2$ , - $CH_2$ (heterocyclyl),

- $CH_2$ (substituted heterocyclyl), -(heterocyclyl),

or - (substituted heterocyclyl);

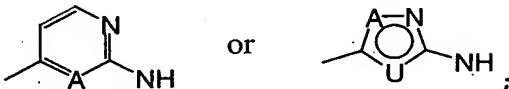
each  $R^3$  is independently selected from hydrogen, R,

$COR$ ,  $CO_2R$  or  $S(O)_2R$ ;

$G$  is R or  $Ar^1$ ;

Ar<sup>1</sup> is aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, or substituted heterocyclyl, wherein Ar<sup>1</sup> is optionally fused to a partially unsaturated or fully unsaturated five to seven membered ring containing zero to three heteroatoms;

Q-NH is



wherein the H of Q-NH is optionally replaced by R<sup>3</sup>;

A is N or CR<sup>3</sup>;

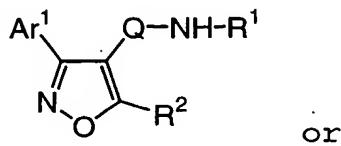
U is CR<sup>3</sup>, O, S, or NR<sup>3</sup>;

Ar<sup>2</sup> is aryl, substituted aryl, heterocyclyl or substituted heterocyclyl, wherein Ar<sup>2</sup> is optionally fused to a partially unsaturated or fully unsaturated five to seven membered ring containing zero to three heteroatoms;

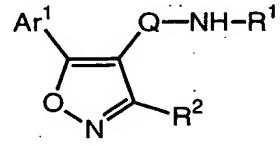
wherein each substitutable carbon atom in Ar<sup>2</sup>, including the fused ring when present, is optionally and independently substituted by halo, R, OR, SR, OH, NO<sub>2</sub>, CN, NH<sub>2</sub>, NHR, N(R)<sub>2</sub>, NHCOR, NHCONHR, NHCON(R)<sub>2</sub>, NRCOR, NHCO<sub>2</sub>R, CO<sub>2</sub>R, CO<sub>2</sub>H, COR, CONHR, CON(R)<sub>2</sub>, S(O)<sub>2</sub>R, SONH<sub>2</sub>, S(O)R, SO<sub>2</sub>NHR, or NHS(O)<sub>2</sub>R, and wherein each saturated carbon in the fused ring is further optionally and independently substituted by =O, =S, =NNHR, =NNR<sub>2</sub>, =N-OR, =NNHCOR, =NNHCO<sub>2</sub>R, =NNHSO<sub>2</sub>R, or =NR; and wherein each substitutable nitrogen atom in Ar<sup>2</sup> is optionally substituted by R, COR, S(O)<sub>2</sub>R, or CO<sub>2</sub>R.

2. The compound of claim 1 where G is Ar<sup>1</sup>.

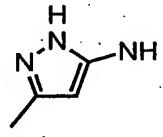
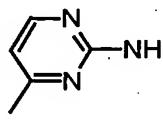
3. The compound of claim 2 having the formula



or



4. The compound of claim 3 where Q-NH is selected from:



, or

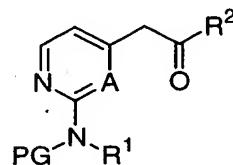
5. The compound of claim 4 where R¹ is alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, pyridinylalkyl, alkoxycycloalkyl, cycloalkyl, alkoxycarbonylcycloalkyl, hydroxycycloalkyl, Ar² or T-Ar² where T is C(=O).

6. The compound of claim 5 where R¹ is cyclohexyl, cyclohexanol-4-yl, cyclohexanon-4-yl, 2-propan-1-ol, 2-methoxy-1-methylethyl, 3-butyryl alkyl ester, 2-pyridinyl-2-ethyl, or an optionally substituted phenyl, naphthyl, pyridyl, quinolinyl, thienyl or indanyl.

7. The compound of claim 6 where R² is an optionally substituted alkyl.

8. A compound selected from those listed in any of Tables 1-7.

9. A compound having the formula:



wherein

A is N or CH;

PG is hydrogen or a nitrogen protecting group;

R<sup>1</sup> is H, T<sub>(n)</sub>-R, or T<sub>(n)</sub>-Ar<sup>2</sup>;

R is an aliphatic or substituted aliphatic group;

n is zero or one;

T is C(=O), CO<sub>2</sub>, CONH, S(O)<sub>2</sub>, S(O)<sub>2</sub>NH, COCH<sub>2</sub> or CH<sub>2</sub>;

and

each R<sup>2</sup> is independently selected from hydrogen, -R,

-CH<sub>2</sub>OR, -CH<sub>2</sub>OH, -CH=O, -CH<sub>2</sub>SR, -CH<sub>2</sub>S(O)<sub>2</sub>R,

-CH<sub>2</sub>(C=O)R, -CH<sub>2</sub>CO<sub>2</sub>R, -CH<sub>2</sub>CO<sub>2</sub>H, -CH<sub>2</sub>CN, -CH<sub>2</sub>NHR,

-CH<sub>2</sub>N(R)<sub>2</sub>, -CH=N-OR, -CH=NNHR, -CH=NN(R)<sub>2</sub>,

-CH=NNHCOR, -CH=NNHCO<sub>2</sub>R, -CH=NNHSO<sub>2</sub>R, -aryl,

-substituted aryl, -CH<sub>2</sub>(aryl), -CH<sub>2</sub>(substituted

aryl), -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>NHCOR, -CH<sub>2</sub>NHCONHR,

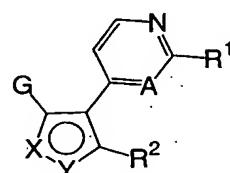
-CH<sub>2</sub>NHCON(R)<sub>2</sub>, -CH<sub>2</sub>NRCOR, -CH<sub>2</sub>NHCO<sub>2</sub>R, -CH<sub>2</sub>CONHR,

-CH<sub>2</sub>CON(R)<sub>2</sub>, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>(heterocyclyl),

-CH<sub>2</sub>(substituted heterocyclyl), -(heterocyclyl),

or -(substituted heterocyclyl).

10. A compound having the formula:



wherein:

X-Y is N-O or O-N providing an isoxazole or reverse isoxazole ring;

A is N or CH;

G is R, aryl or substituted aryl;

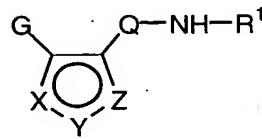
R is aliphatic or substituted aliphatic

R<sup>2</sup> is selected from hydrogen, -R, -CH<sub>2</sub>OR, -CH<sub>2</sub>OH, -CH=O, -CH<sub>2</sub>SR, -CH<sub>2</sub>S(O)<sub>2</sub>R, -CH<sub>2</sub>(C=O)R, -CH<sub>2</sub>CO<sub>2</sub>R, -CH<sub>2</sub>CO<sub>2</sub>H, -CH<sub>2</sub>CN, -CH<sub>2</sub>NHR, -CH<sub>2</sub>N(R)<sub>2</sub>, -CH=N-OR, -CH=NNHR, -CH=NN(R)<sub>2</sub>, -CH=NNHCOR, -CH=NNHCO<sub>2</sub>R, -CH=NNHSO<sub>2</sub>R, -aryl, -substituted aryl, -CH<sub>2</sub>(aryl), -CH<sub>2</sub>(substituted aryl), -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>NHCOR, -CH<sub>2</sub>NHCONHR, -CH<sub>2</sub>NHCON(R)<sub>2</sub>, -CH<sub>2</sub>NRCOR, -CH<sub>2</sub>NHCO<sub>2</sub>R, -CH<sub>2</sub>CONHR, -CH<sub>2</sub>CON(R)<sub>2</sub>, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>(heterocyclyl), -CH<sub>2</sub>(substituted heterocyclyl), -(heterocyclyl), or -(substituted heterocyclyl); and

R<sup>1</sup> is selected from halogen, NH<sub>2</sub>, SR, or SO<sub>2</sub>R; provided that R<sup>1</sup> is other than Br or Cl when A is CH.

11. A pharmaceutical composition comprising an amount of a compound according any one of claims 1-8 effective to inhibit JNK, and a pharmaceutically acceptable carrier.

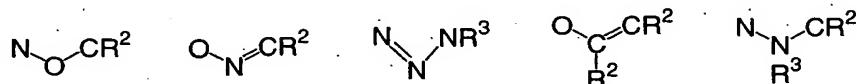
12. A method for treating a disease state or condition in mammals that is alleviated by treatment with a protein kinase inhibitor, comprising administering to a mammal in need of such a treatment a therapeutically effective amount of a compound of formula I:



I

wherein:

X-Y-Z is selected from one of the following:



R<sup>1</sup> is H, CONH<sub>2</sub>, T<sub>(n)</sub>-R, or T<sub>(n)</sub>-Ar<sup>2</sup>;

R is an aliphatic or substituted aliphatic group;

n is zero or one;

T is C(=O), CO<sub>2</sub>, CONH, S(O)<sub>2</sub>, S(O)<sub>2</sub>NH, COCH<sub>2</sub> or CH<sub>2</sub>;  
each R<sup>2</sup> is independently selected from hydrogen, -R,

-CH<sub>2</sub>OR, -CH<sub>2</sub>OH, -CH=O, -CH<sub>2</sub>SR, -CH<sub>2</sub>S(O)<sub>2</sub>R,

-CH<sub>2</sub>(C=O)R, -CH<sub>2</sub>CO<sub>2</sub>R, -CH<sub>2</sub>CO<sub>2</sub>H, -CH<sub>2</sub>CN, -CH<sub>2</sub>NHR,

-CH<sub>2</sub>N(R)<sub>2</sub>, -CH=N-OR, -CH=NNHR, -CH=NN(R)<sub>2</sub>,

-CH=NNHCOR, -CH=NNHCO<sub>2</sub>R, -CH=NNHSO<sub>2</sub>R, -aryl,

-substituted aryl, -CH<sub>2</sub>(aryl), -CH<sub>2</sub>(substituted aryl), -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>NHCOR, -CH<sub>2</sub>NHCONHR,

-CH<sub>2</sub>NHCON(R)<sub>2</sub>, -CH<sub>2</sub>NRCOR, -CH<sub>2</sub>NHCO<sub>2</sub>R, -CH<sub>2</sub>CONHR,

-CH<sub>2</sub>CON(R)<sub>2</sub>, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>(heterocyclyl),

-CH<sub>2</sub>(substituted heterocyclyl), -(heterocyclyl),

or -(substituted heterocyclyl);

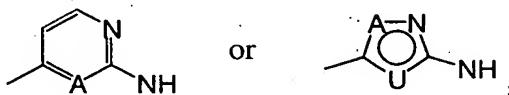
each R<sup>3</sup> is independently selected from hydrogen, R,

COR, CO<sub>2</sub>R or S(O)<sub>2</sub>R;

G is R or Ar<sup>1</sup>;

Ar<sup>1</sup> is aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, wherein Ar<sup>1</sup> is optionally fused to a partially unsaturated or fully unsaturated five to seven membered ring containing zero to three heteroatoms;

Q-NH is



wherein the H of Q-NH is optionally replaced by R<sup>3</sup>;

A is N or CR<sup>3</sup>;

U is CR<sup>3</sup>, O, S, or NR<sup>3</sup>;

Ar<sup>2</sup> is aryl, substituted aryl, heterocyclyl or substituted heterocyclyl, wherein Ar<sup>2</sup> is optionally fused to a partially unsaturated or fully unsaturated five to seven membered ring containing zero to three heteroatoms;

wherein each substitutable carbon atom in Ar<sup>2</sup>, including the fused ring when present, is optionally and independently substituted by halo, R, OR, SR, OH, NO<sub>2</sub>, CN, NH<sub>2</sub>, NHR, N(R)<sub>2</sub>, NHCOR, NHCONHR, NHCON(R)<sub>2</sub>, NRCOR, NHCO<sub>2</sub>R, CO<sub>2</sub>R, CO<sub>2</sub>H, COR, CONHR, CON(R)<sub>2</sub>, S(O)<sub>2</sub>R, SONH<sub>2</sub>, S(O)R, SO<sub>2</sub>NHR, or NHS(O)<sub>2</sub>R, and wherein each saturated carbon in the fused ring is further optionally and independently substituted by =O, =S, =NNHR, =NNR<sub>2</sub>, =N-OR, =NNHCOR, =NNHCO<sub>2</sub>R, =NNHSO<sub>2</sub>R, or =NR; and wherein each substitutable nitrogen atom in Ar<sup>2</sup> is optionally substituted by R, COR, S(O)<sub>2</sub>R, or CO<sub>2</sub>R.

13. The method of claim 12 wherein the disease state is alleviated by treatment with an inhibitor of JNK.

14. The method of claim 12 wherein the disease is selected from inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative

diseases, allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or conditions associated with proinflammatory cytokines.

15. The method according to claim 12, wherein said method is used to treat or prevent an inflammatory disease selected from acute pancreatitis, chronic pancreatitis, asthma, allergies, or adult respiratory distress syndrome.

16. The method according to claim 12, wherein said method is used to treat or prevent an autoimmune disease selected from glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

17. The method according to claim 12, wherein said method is used to treat or prevent a destructive bone disorders selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.

18. The method according to claim 12, wherein said method is used to treat or prevent a

proliferative disease selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, or multiple myeloma.

19. The method according to claim 12, wherein said method is used to treat or prevent neurodegenerative disease selected from Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia or neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity or hypoxia.

20. The method according to claim 12, wherein said method is used to treat or prevent ischemia/reperfusion in stroke or myocardial ischemia, renal ischemia, heart attacks, organ hypoxia or thrombin-induced platelet aggregation.

21. The method according to claim 12, wherein said method is used to treat or prevent a condition associated with T-cell activation or pathologic immune responses.

22. The method according to claim 12, wherein said method is used to treat or prevent an angiogenic disorder selected from solid tumors, ocular neovascularization, or infantile haemangiomas.

23. The method of claim 12 wherein the disease state or condition is alleviated by treatment with an inhibitor of a Src-family kinase.

24. The method of claim 23 wherein the disease state or condition is hypercalcemia, restenosis, hypercalcemia, osteoporosis, osteoarthritis, symptomatic treatment of bone metastasis, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, Hashimoto's thyroiditis, Guillain-Barre syndrome, chronic obstructive pulmonary disorder, contact dermatitis, cancer, Paget's disease, asthma, ischemic or reperfusion injury, allergic disease, atopic dermatitis, or allergic rhinitis.